

BLOOD SEDIMENTATION AS A PROGNOSTIC AID.

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During the past few decades medicine has made marked progress. However, the advances have been largely in the realm of diagnosis and treatment. Prognosis remains, as it has been for generations, too largely a matter of individual judgment. The scientific criteria that have been developed to aid the physician have, too often, failed to tell him what progress the disease process was making in the sick individual, or the degree of tissue resistance possessed by the patient. Yet today, as in past generations, the main interest of the sick man, his family and friends, and his medical adviser, also, is not diagnosis *per se*, but: "How ill is the patient? How long is he going to be disabled and what is his chance of recovery? If we were able to answer these questions accurately in the majority of cases, how much more contented we and our patients would be. If we had some measure of the degree of tissue damage, some means of telling us whether the pathological process was on the increase or decrease, how much more efficiently might we utilize the therapeutic agents available.

To be sure, a careful clinical survey of the patient with due regard to temperature, pulse and respiration curves, his weight, digestion, strength, complete blood counts and blood chemistry determinations may reveal to the experienced clinician definite indications of progress which may partially assure him. How much better it would be if he could have some scientific measure of the extent of tissue destruction so that comparative figures might be available from time to time during the illness to indicate the progress of the disease. If such were possible, it would give untold aid in this most difficult field of medicine.

Pathological processes in the body, especially those involving tissue destruction, profoundly alter the body chemistry. The greater the destruction of cells, the more waste products formed. If each organ had some specific type of waste material that could be chemi-

cally identified in the excreta, it might be possible to determine how much tissue destruction was taking place in an involved tissue. Such is impossible today.

Neither do we have available any test that will tell us the intensity of a lesion. In spite of the work of Wright on the opsonins and other investigations along similar lines, the resistance of the patient remains a matter of virtually pure theory. No one actually knows what constitutes resistance. However, certain lesions of the body produce alterations in the blood which can be measured, even though crudely, thus giving us some criteria capable of numerical representation. If these are studied repeatedly, they may aid us in the difficult matter of prognosis. One such test is the relative speed of sedimentation of erythrocytes in blood which has been rendered non-coagulable by the addition of citrate or other such agent.

When Fahraeus, in 1918, proposed this test as a diagnostic point in pregnancy, he was merely reviving an observation mentioned by Hippocrates and Galen. In 1767 John Hunter made extensive studies on this phenomenon, then known as "the crusta phlogistica," and a marked revival of interest in it again occurred in the middle of the nineteenth century. Soon after the report of Fahraeus, it was found that the test was non-specific and occurred not only in pregnancy, but also in virtually all conditions involving extensive cellular disintegration.

Various theories have been propounded to explain the alteration in the rate of sedimentation: changes in electrical potential of the cells, alteration of cell volume or mass, viscosity or chemical variance, etc. Present opinion is that the relative speed of sedimentation of erythrocytes is dependent upon the colloidal chemistry of the blood, and chiefly on the globulin-fibrinogen ratio. In conditions involving rapid destruction of tissue, there is found in the blood an excess of fibrinogen. In any case where the content of fibrinogen in the blood is above normal, the speed of sedimentation is increased. The greater the increase of fibrinogen content, the more rapid the sedimentation rate, so that the two curves run virtually parallel. However, the sedimentation test is so much simpler than a fibrinogen determination, that it is to be preferred in clinical work.

Extensive investigations have shown that age, sex, fever, and

physiological changes in the body (with the exception of pregnancy and menstruation) have but little effect upon the sedimentation rate. Such changes as are produced under these conditions are found to be within narrow limits of the usually assumed normal. Severe anemias may so affect the test as to make it unreliable. Administration of adrenalin and pilocarpin markedly increase the rate. Other drugs seem to have but little effect upon it. With these comparatively few exceptions, the test seems to offer a reliable index of blood fibrinogen formation.

Since an increase of blood fibrinogen is dependent chiefly upon tissue destruction, it follows that an increase in the sedimentation rate gives a measure of the intensity of the pathological processes in the body. Such a test, so simply done, causing so little distress or expense to the patient and yet yielding figures capable of comparison over a period of time should have a wide application in clinical conditions, especially in those diseases known to show constant alterations in the sedimentation rate.

There have been numerous methods proposed to designate the rapidity of sedimentation, but all are based upon the same essential principle. The blood, which has been rendered non-coagulable by some chemical, usually citrate, is placed in a cylinder and the level reached by the surface of the layer of red cells is read at stated intervals and the figures used to plot a curve. Or else, the final sedimentation point is noted and the total time elapsing to reach it is used for the figure. At the present time, some modification of the former method is most widely used. In our laboratory, the method of Cutler is the one in use and has served to give us information we feel is of definite value. The test is simple, is completed in one hour, and the curves obtained may be classified under four general types. It gives also a figure as a final reading that may be used in charting the test over a long series of readings. The technique is discussed in virtually all modern laboratory manuals and will not be further elaborated here since this is a clinical and not a laboratory review.

During the past fifteen years, a mass of literature on the test has been assembled, chiefly in European publications, but little has been written on the test as a prognostic aid, except in a few fields. Following its introduction into obstetrics, it was quickly adapted to

gynecology and, to the present time, its chief advocates have been the gynecologists and surgeons and the phthisiotherapists. It is the hope of the writer that it may be utilized to a greater extent in general medicine as a method of value in helping to determine prognosis.

One of the authors most enthusiastic in its use is Polak,¹ who considers it will tell the presence of pus before the pulse, temperature or white count will. He thinks it will give definite indication of the time for elective operations, indicate the need for drainage and give prognosis of complications. Baer² states that the sedimentation rate is a more delicate prognostic index than the white count or the temperature curve. It is also better to determine the presence of infection. Friedlander³ says it is a more reliable index of infection than the white count, pulse or temperature and, as a prognostic agent, its value is almost unlimited. Mathieu⁴ says in salpingitis it is more sensitive than the pulse, white count and temperature; that it shows the progress of the case and one should not operate until the sedimentation rate has become normal. Forestier⁵ believes a high sedimentation rate means pus even though the pulse, temperature and white count are normal and no mass can be felt. He thinks it is a good index as to the efficiency of drainage and, properly used post-operatively, will warn of septic complications. Adams⁶ feels it is less valuable than other tests to determine the presence of appendix infection and that a high rate means the absorption of toxic products, not mere infection. He also feels it is the most reliable test to determine the time to operate pelvic infections.

In malignant conditions, Rubin⁷ has found it a good index of the patient's condition. The rate varies with the rapidity of progression of the tumor, the severity of the process and the constitutional reaction of the patient. Rosenthal⁸ states that the rate is rapid in carcinoma and in infectious jaundice, but normal or slow in non-infectious jaundice. Forestier⁵ states that, in cachectic states, the rate may be low from liver involvement, thus lowering the blood fibrinogen. Practically all investigators have found low rates prevailing in icterus, and in such cases the test is of little help in prognosis.

In tuberculosis there has been much work done in the use of this test in prognosis. Cutler⁹ is most enthusiastic over its value as a prognostic agent. He thinks it often more dependable than any

other subjective or objective finding. It is a measure of pathologic activity like leucocytosis and, when tissue destruction is more rapid than usual, the speed of the sedimentation is in direct proportion to the activity of the disease. He believes it will estimate activity in tuberculosis in a scientific manner and is indispensable in substituting fact for opinion. When compared with a group of criteria commonly used for the estimation of activity in this disease, it proved the most accurate of any, being correct in 88% of all cases. When borderline cases were omitted, it proved 100% correct, so he feels that clinical judgment might have been at fault in one half of the cases where agreement was not reached, so that the test should be considered as 94% accurate in the prognosis of tuberculosis. Trail¹⁰ says it is of value in watching the progress of a case and that "the test is of outstanding assistance to the clinician in his most difficult tasks — evaluation of treatment and formulation of prognosis." Davies¹¹ thinks it has its greatest value as a prognostic aid when compared to the clinical course. To him it has definite prognostic value, and may warn of approaching complications. Townsend¹² states that, while not specific, it parallels the severity of the disease, but is not an index of the extent of involvement. Graefe, quoted by Levinson,¹³ states that small doses of tuberculin in incipient cases may increase the sedimentation rate without affecting the temperature or pulse. Banyai¹⁴ believes no tuberculous patient should be discharged until the rate is normal. Cases with positive sputum and a normal sedimentation rate usually do well, since they seem to have a high resistance. A single test is only suspicious, but repeated high rates have value. Briskman¹⁵ states the test's value is in denoting activity and determining progress, especially in monthly rechecks. He has never had a tuberculous patient die with a normal sedimentation. In a personal communication, he states that he believes the test to be of extreme value in determining when a case is ready for discharge and would hesitate to dismiss a patient with a high sedimentation rate even though all other signs and symptoms were favorable.

Among the other phthisiotherapists of Colorado Springs the same opinion is largely held. The test is becoming more widely used in Colorado in recent years and the majority of men using it as a routine are enthusiastic concerning its value in tuberculosis.

In acute rheumatic fever, the general opinion is that it is of

inestimable aid in determining not only the progress of the disease, but also its point of termination. Ernestine¹⁶ believes it a more sensitive criterion of activity of rheumatic process than the leucocyte count. The fact that the sedimentation rate may remain abnormal long after the white blood count is normal may mean persistence of a low grade infection, and the infection is not to be considered arrested until the sedimentation rate reaches and remains normal.

Kahlmeter¹⁷ agrees and feels that physiotherapy should not be started until the rate is normal. Ernestine further states that the sedimentation rate is not affected by drugs as is the white count and in relapses its change is greater than the change in the count. He feels that a sedimentation rate should be taken in all cases of rheumatic fever at regular intervals of four to seven days after the white count has fallen below 9000 until the sedimentation rate has become normal. Forestier⁵ advises keeping the patient in bed until the rate is normal if one would avoid complications. Weiss¹⁸ states that severe joint symptoms do not necessarily mean a high rate and that in mild cases the rate does not return to normal sooner than in severe. Usually the sedimentation rate does not return to normal until three to five weeks after the fever and leucocytosis have ceased. He feels that, judging by the sedimentation rate, this disease does not tend to become chronic. He feels that in this disease the presence of anemia makes the rate not reliable.

In cases of infectious arthritis there is a slightly different situation. Here the rate is high, irrespective of the causative organism, according to Weiss, and the severity of the case is not paralleled by the degree of increase in the rate. He believes that the rate will remain fast until the cause is found and removed. He quotes Meero-vitch that cases released from treatment before the rate has returned to normal will suffer a relapse. Sharpless¹⁹ states that, in gonococcal arthritis, the rate reaches normal more quickly than in rheumatic fever, possibly because of the lack of cardiac complications.

In extra-articular rheumatoid conditions, Forestier⁵ has found that a high rate means a focus of infection and that the condition will persist until the source is eradicated. Sharpless¹⁹ has found the same to be true in arthritis deformans and sciatica.

In the realm of general medicine, less has been done with the use of the test as a prognostic measure. Schloss²⁰ believes there is a

certain correlation between the sedimentation rate and quantitative tissue destruction, and that the disease must be known to determine pathologic activity by its use. Peterman²¹ believes other findings of greater value, but that a high rate demands further study of the case. Wingfield²² thinks the test is of little value if it is possible to give a close observation, but when that is not possible it is of value in prognosis. However, he feels that the test is non-specific and not delicate.

In coronary thrombosis Rabinowitz²³ has found that the rate becomes rapid three to five days following the attack and remains abnormal longer than the temperature or white count. He feels that the test is an index of repair process and that the infarctive reaction has not subsided until the sedimentation rate has approached normal. It is thus an indication of the need for continuous bed rest and the patient should not be allowed up until the rate is normal.

Forestier⁷ feels that the test follows the temperature curve, but is later in developing and lasts longer. A simple coryza will occasion a rise lasting for two weeks and influenza will cause a slight increase that will not return to normal for four to six weeks following recovery. He feels that by the use of this test, it is possible to differentiate true Parkinson's disease, which has a high rate, from post-encephalitic parkinsonism, which has a low rate.

The majority of authors cited herein agree that the test has some value, especially when done repeatedly on the same patient. A persistent high reading means an extensive disease or one which has not subsided. Consistently falling readings indicate that the process is abating and give a good prognosis, while a rising rate indicates progression of the lesion or the development of a complication.

Unfortunately the test does not give information in all disease processes, but there are sufficient pathological conditions where it is applicable to afford the clinician real aid. To be sure, it is not to be considered an infallible index of prognosis, but merely another test to add to those already in use to help give us a more complete picture of the condition of the patient.

An enumeration of some of the conditions in which the test gives consistently high readings follows: tuberculosis, arthritis, chronic septic processes, malignancies undergoing necrosis, pregnancy after the third month, menstruation, diabetes, florid syphilis, asthma,

pneumonia, malaria, malignant endocarditis, septicaemia, leukaemia, Addison's disease, arteriosclerosis, paresis, senile dementia, epilepsy (especially after the seizure), tubal pregnancy and the exanthemata.

Conditions in which the rate is ordinarily not high are: early carcinoma, gall stones, severe liver degenerations, icterus, non-inflammatory pelvic tumors (unless undergoing degeneration or necrosis), cardiac stasis, cardio-vascular disease, gout, endocrine disorders, paranoia, manic depressive insanity, psychopathies and hysteria.

Here then is a test that is easily performed by any physician, without calling for extensive laboratory equipment, causing little trouble or expense to the patient, yet giving an indication of tissue change in a form that can be charted graphically so as to permit comparison with later tests. The extent of the reaction is dependent upon tissue destruction through the increased formation of fibrinogen in the blood. Should the disease continue to progress, the increased formation of fibrinogen will be reflected as a rapid sedimentation. Should repair processes exceed the destructive lesion, the test will show a falling rate.

While the test has been much used in experimental work and its limitations fully noted, yet its use in clinical medicine has been somewhat limited. With the exception of the gynecologists and surgeons and the phthisiotherapists few of the branches of medicine have made use of the test to determine the intensity and direction of progress of their cases. It is our belief that this test is worthy of more use in general medical conditions, especially those in which there is an alteration of marked degree in the test during the acute stages. A rapid rate is indicative that the lesion is still producing cell destruction to excess, and repeated tests may be compared numerically to show progress. It is thus one more test to aid us in our most difficult and at the same time most important task—prognosis.

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DISCUSSION.

PRESIDENT HAMMAN: Dr. Heise, who was to have opened up the discussion on this paper, was unable to come to the meeting, but he sent some remarks which Dr. Packard will read.

[Dr. Packard read the written discussion of Dr. Heise.]

DR. HEISE: Dr. Bortree has just given you a very excellent exposition of the blood sedimentation test and the probable reasons for its occurrence. The test is not specific and occurs in a variety of diseases.

At the Trudeau Sanatorium the sedimentation test has been done by Dr. Albert G. Hahn, who has made many hundreds of tests, many of which have been repeats, using the method of Westergren. While the Cutler method is perhaps a better one for a graphic representation, we have not done a sufficient number to determine whether it is of greater value. The sedimentation test is valuable in tuberculosis as it seems to portray the allergic reaction of the disease; in other words, gives evidence of destruction of tissue, as Dr. Bortree has already explained. In evidence of this we find that when the sedimentation rate upon admission of a patient is at or about normal, relapse of the disease is rather infrequent during the average six or seven months' stay of an individual in Trudeau.

If we divide the sedimentation rates into three classes, say from 0 to 10, 10 to 20, and above 20 mm. per hour, we note that as the sedimentation rate increases the proportion of those with positive sputum and those with definite evidence of X-ray cavity increases, showing that when destruction about the focus occurs the sedimentation rate is likely to increase. Likewise in these three groups we find that the highest percentage of minimal lesions occurs in those of the first group, *i.e.*, 0 to 10 mm.; and that in the third group, 20 and above, there are comparatively few minimal lesions. Furthermore, in patients with

increased sedimentation rate, the per cent of relapses of these diseases increases, and it is thought that an increasing number of patients need interference or collapse therapy to overcome their disease.

A single test is by no means conclusive; nevertheless a single test does give an idea of the reaction about the focus in the lung or elsewhere in the body and, strangely enough, even several years after the original sedimentation test was done, we have found an increased percentage of relapses after discharge from the sanatorium among those who originally showed a rapid sedimentation.

At times an increased sedimentation rate will call your attention to disease elsewhere than in the lungs. This has happened in several instances in Trudeau when the pulmonary picture was that of quiescence but the sedimentation rate increased. Later on an extrapulmonary tuberculosis developed in an acute form, such as tuberculous peritonitis. At other times an increased sedimentation rate will occur before the onset of acute symptoms, such as pleurisy with effusion, etc.

While the sedimentation rate, the Medlar cell count and the filament-nonfilament tests react more or less the same in the same individual, nevertheless there are enough variations to indicate that they are not dependent entirely upon one and the same thing. When properly done the sedimentation test is simple and the most practical of the three, and justifies its use in all cases. Portraying as it does destruction of tissue cells, it warns of the unstable lesion.

Repeated tests may well be used to control collapse therapy, exercise and other forms of treatment.

DR. JOSEPH S. PRATT: I would like to ask Dr. Bortree if he has examined the blood fasting or at any time during the day. If he has done it fasting, I would like him to compare it with the examinations at the other times. Has he found the difference significant?

I hope some others who have used this test in connection with the diagnosis and treatment of pulmonary tuberculosis will give their conclusions. It has seemed to my very limited experience that it might have value, but I am not familiar with the literature.

Recently I had a case of a man who had apparently arrested pulmonary tuberculosis. I saw him in the fall and his sedimentation rate was 3 mm. per hour. This spring I saw him again and the blood at that time was normal. Clinically he had no evidence of pulmonary tuberculosis. The lungs were unchanged on physical examination, but the X-ray indicated a slight increase of the shadows, and the blood sedimentation test, not fasting, taken two o'clock in the afternoon in both instances, had risen to 16. I would like to know if Dr. Bortree would consider that significant. It seemed to me there was no elevation in pulse or temperature.

I have thought that it might be of value in many diseases in determining whether we needed to keep the patient quiet and at rest. A year ago I was consulted by a man who had recovered from a simple common cold, but his strength had not returned, he was feeling badly, was nervous, and on physical examination I could find nothing wrong with him. The sedimentation test, however, was significant. The sedimentation was very rapid, 40 or 50 mm. in an

hour, and it seemed to me wise under those conditions to keep him quiet, which I did for almost a month, and it took that time before the sedimentation returned to normal.

I would like to ask Dr. Bortree if, from his studies, it is true that after a simple respiratory infection, non-tuberculous, you find a marked increase in sedimentation time which is kept up for weeks or for a long time after the clinical symptoms have disappeared.

I had one case of arthritis in a very much overworked man, who had been for three years in Cuba. He improved last summer in nearly every respect, although he still had some pain on his hip, but I would have been inclined to think that his symptoms were not serious if it had not been for the fact that his sedimentation time was very rapid. I advised him to return to his home in New Mexico and to keep very quiet for months; in fact, until his sedimentation time was all right. I had a letter from him sometime later and he said that he was feeling perfectly well and that he thought he was able to go back to work, and that a recent test of his sedimentation time had shown that it was normal.

DR. LAWRASON BROWN: I enjoyed very much the paper that was presented by Dr. Bortree. I think the test has helped us considerably, though of course we all know that these tests have certain limits.

Recently I had a case which interested me a good deal. The patient was a man who was a professor in one of the universities in New York, who had taken treatment for tuberculosis for some time, returned home, and did well for some months. Then he became exceedingly nervous. He saw some of the specialists in New York who could detect no change on the X-ray films or from physical examination, and who decided he was simply nervous. They told that to his family, and this almost produced a divorce.

He came back to Saranac Lake. I saw him and I had to agree there was no change on the X-ray film, no change in the physical signs, and then I thought that I would test his blood. He had a sedimentation test done and it was one of those indefinite ones between 10 and 20, and we couldn't say very much about it. Then I suggested to him that when he return he see Dr. Sabin. Dr. Sabin studied his blood and told him that he was on the verge of a very severe relapse. This frightened him more than he already was, and he returned at once to Saranac Lake and then for the first time in the history of his case he showed bacilli in his sputum.

DR. DAVID RUSSELL LYMAN: I wanted to ask one question: What experience Dr. Bortree has had in helping him differentiate between tuberculosis and the new growth of the lung. We have had several cases where we felt that the very high rate of sedimentation was entirely out of proportion with what we ordinarily expected with the clinical symptoms of tuberculosis in cases sent in with supposed tuberculosis, and this very high rate of sedimentation first attracted our attention to the possibility of new growth.

DR. FRANCIS B. TRUDEAU: I should like to ask of Dr. Bortree one or two questions: What is his idea of the normal in tubercular cases, and also what

effect he finds menstruation has on the sedimentation rate. Is it not usually higher at this time?

DR. EDGAR MAYER: I would like to add to what Dr. Bortree has said. We have done over a thousand at our sanatorium at Saranac Lake and we found them of considerable value. Just to add one case in corroboration of Dr. Bortree's description, we had one girl that had been seen by a rather prominent internist in New York, and I also had seen her. She consulted us on the advisability of marriage. We all decided that, although everything was negative, on account of a high sedimentation rate she should wait. She insisted on going through with her engagement and was married. Within two months she had quite a marked hemoptysis.

DR. BORTREE: I rather sketchily went over this subject today, hesitating to waste more of your time than was necessary, and some of the points which are covered in the written paper I failed to mention.

In the first place I want to thank the gentlemen for their interest in this paper.

On Dr. Pratt's question concerning the fasting rate, the difference in the rate while fasting and with food is so slight as to come within the ordinary arbitrarily assumed normal limits. With the exception of menstruation and pregnancy, no other physiological process influences the rate markedly enough to alter your judgment by it.

Dr. Pratt's question of the man coming to him with a rate of 3 and later having a rate of 16 would be of definite significance. A single rate, unless extremely abnormal, should not be considered greatly, but repeated tests on the same individual under comparable circumstances may give you definite indications. While the 16 rate is not high, it is a definite increase and it is an evidence that cellular activity is greater than it should be, and it should be a warning signal.

I think probably every person in this room has had a common cold, and everyone knows how you feel for a week or so after a common cold, and your patients know how it feels as well. If you have the flu you know that it takes a longer period before you begin feeling like yourself, which is very hard to make some patients realize.

The next time you have a common cold, have a sedimentation test done about every four days for two weeks, and you will find undoubtedly you have a rapid sedimentation time. If, however, you have the flu, you will find that the sedimentation rate will remain abnormally high from three to six weeks. In other words, the patient's resistance is not back to normal and his condition is reflected by his sedimentation rate for a period exceeding that following an acute cold.

Dr. Lyman's experience with new growths in the lung is comparable with ours. As you probably remember, one of the best artificial coagulants that we can use is prepared from lung tissue, so everything which causes rapid changes or destruction of lung tissue increases the fibrillation of the blood, therefore pulmonary neoplasms will give an extremely rapid rate.

Dr. Trudeau's question as to the normal in tuberculosis, I can't answer. I know not what the normal is in the tubercular case. It goes back to the same old question. This test while not specific is merely one more indication to tell you a bit of what is going on within the patient, how the patient is being affected by the disease, and it will help you in treatment.

Menstruation produces a very rapid rate, and our technicians are familiar with the phenomenon. Two days before I started for the meeting I called for a blood sedimentation test on one of my patients. The technician called me up and said, "You don't want a sedimentation test on that girl; she's menstruating." (Applause.)